

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
16 October 2003 (16.10.2003)

PCT

(10) International Publication Number
WO 03/084502 A1

(51) International Patent Classification⁷: A61K 9/00,
31/46, A61M 15/00

Bernd [DE/DE]; Goethestrasse 1, 55411 BINGEN AM
RHEIN (DE).

(21) International Application Number: PCT/EP03/03431

(74) Common Representative: BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG; Binger Strasse 173, 55216 INGELHEIM (DE).

(22) International Filing Date: 2 April 2003 (02.04.2003)

(81) Designated States (national): AE, AG, AL, AM, AT, AU,

AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,

GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,

MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,

SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,

UZ, VC, VN, YU, ZA, ZM, ZW.

(25) Filing Language: English

(84) Designated States (regional): ARIPO patent (GH, GM,

KE, LS, MW, MZ, SD, SL, TZ, UG, ZM, ZW),

Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

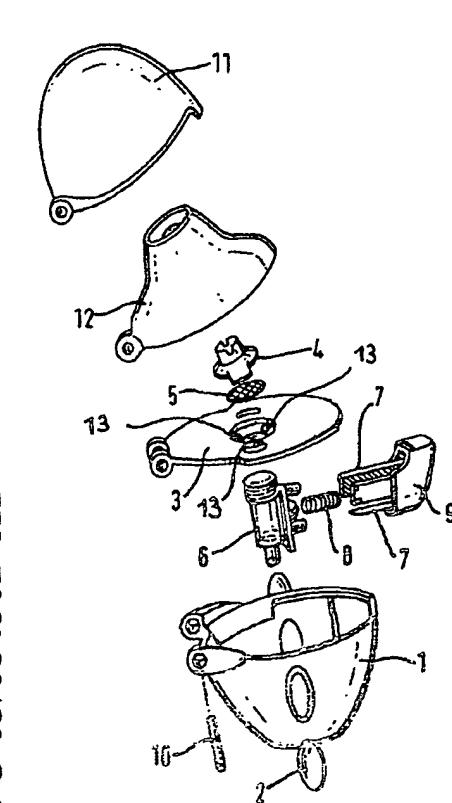
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,

ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,

(26) Publication Language: English

[Continued on next page]

(54) Title: INHALATION KIT COMPRISING INHALABLE POWDER OF TIOTROPIUM



WO 03/084502 A1

(57) Abstract: The invention relates to a method for the administration of powdered preparations containing tiotropium via inhalation.



SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Published:

— *with international search report*

PATENT COOPERATION TREATY

PCT

REC'D 25 JUL 2003

WIPO PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1-1323-PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/03431	International filing date (day/month/year) 02/04/2003	(Earliest) Priority Date (day/month/year) 09/04/2002
Applicant BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **8** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. Unity of Invention is lacking (see Box II).

4. With regard to the title,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

INHALATION KIT COMPRISING INHALABLE POWDER OF TIOTROPIUM

5. With regard to the abstract,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

1

None of the figures.

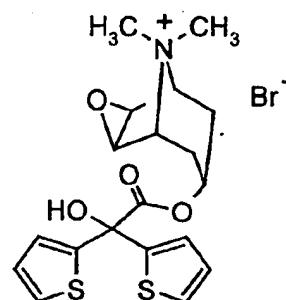
**INHALATION KIT COMPRISING INHALABLE
POWDER OF TIOTROPIUM**

The invention relates to a method for the administration of powdered preparations containing tiotropium by inhalation.

5

Background to the invention

Tiotropium bromide is known from European Patent Application EP 418 716 A1 and has the following chemical structure:



10

Tiotropium bromide is a highly effective anticholinergic with a long-lasting activity which can be used to treat respiratory complaints, particularly COPD (chronic obstructive pulmonary disease) and asthma. The term tiotropium refers to the free ammonium cation.

15

For treating the abovementioned complaints, it is useful to administer the active substance by inhalation. In addition to the administration of broncholytically active compounds in the form of metered aerosols and inhalable solutions, the use of inhalable powders containing active substance is of particular importance.

20

With active substances which have a particularly high efficacy, only small amounts of the active substance are needed per single dose to achieve the desired therapeutic effect. In such cases, the active substance has to be diluted with suitable excipients in order to prepare the inhalable powder. Because of the large amount of excipient,

25

the properties of the inhalable powder are critically influenced by the choice of excipient. When choosing the excipient its particle size is particularly important. As a rule, the finer the excipient, the poorer its flow properties. However, good flow properties are a prerequisite for highly accurate metering when packing and dividing up the individual doses of preparation, e.g. when producing capsules for powder

30

inhalation or when the patient is metering the individual dose before using a multi-dose inhaler. It has also been found that the particle size of the excipient has a considerable influence on the proportion of active substance in the inhalable powder

which is delivered for inhalation. The term inhalable proportion of active substance refers to the particles of the inhalable powder which are conveyed deep into the branches of the lungs when inhaled with a breath. The particle size required for this is between 1 and 10 μm , preferably less than 5 μm .

5

Finally, it has been found that the intended therapeutic effect upon the administration of a pharmaceutical composition via inhalation can be decisively influenced by the inhalation device.

10 Accordingly, the aim of the invention is to provide for a therapeutically efficient method for the administration of inhalable powders containing tiotropium. Another object of the invention is to provide for an inhalation kit comprising a tiotropium containing powder and an inhalation device, said kit being applicable in the method for administration mentioned before.

15

Detailed description of the invention

In the method according to the invention an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient is administered.

20

Of particular interest for the method according to the invention is an inhalable powder containing 0.01 to 2 %, preferably 0.04 to 0.8 %, more preferably 0.08 to 0.64 % tiotropium in admixture with a physiologically acceptable excipient is administered.

More preferably in the method according to the invention an inhalable powder

25 containing 0.1 to 0.4 % tiotropium in admixture with a physiologically acceptable excipient is administered.

By tiotropium is meant the free ammonium cation. The counter-ion (anion) may be chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate. Of these anions, the bromide is preferred.

Accordingly, the method according to the present invention preferably relates to inhalable powders which contain tiotropium in form of tiotropium bromide in an amount of 0.0012 to 6.02 %, in admixture with a physiologically acceptable excipient.

Of particular interest for the method according to the invention is an inhalable powder 35 containing 0.012 to 2.41 %, preferably 0.048 to 0.96 %, more preferably 0.096 to 0.77 % tiotropium bromide in admixture with a physiologically acceptable excipient is administered.

More preferably in the method according to the invention an inhalable powder containing 0.12 to 0.48 % tiotropium bromide in admixture with a physiologically acceptable excipient is administered.

- 5 Tiotropium bromide is, depending on the choice of reaction conditions and solvents, obtainable in different crystalline modifications. Most preferred according to the invention are those powder preparations, that contain tiotropium in form of the crystalline tiotropium bromide monohydrate. Accordingly, the powdered preparations obtainable according to the invention preferably contain 0.0012 to 6.25 % crystalline tiotropium bromide monohydrate in admixture with a physiologically acceptable excipient is administered. Of particular interest for the method according to the invention is an inhalable powder containing 0.0125 to 2.5 %, preferably 0.05 to 1 %, more preferably 0.1 to 0.8 % crystalline tiotropium bromide monohydrate in admixture with a physiologically acceptable excipient is administered.
- 10 15 More preferably in the method according to the invention an inhalable powder containing 0.12 to 0.5 % crystalline tiotropium bromide monohydrate in admixture with a physiologically acceptable excipient is administered.
- 15

Examples of physiologically acceptable excipients which may be used to prepare the inhalable powders applicable according to the invention include, for example, monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextrane), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates, preferably in the form of their monohydrates.

In the method according to the invention the average particle size of the physiologically acceptable excipient is preferably between 10 to 500 μm , more preferably between 15 to 200 μm , most preferably between 20 to 100 μm . If not otherwise emphasized the term average particle size according to the invention is to be understood as the Mass Median Aerodynamic Diameter (MMAD). Methods for the determination thereof are known in the art. Besides the coarser particle fraction of the excipient mentioned hereinbefore, the excipient can optionally additionally contain a specifically added fraction of excipient of finer particle size. This finer particle size fraction is characterized by an average particle size of 1 to 9 μm , preferably 2 to 8 μm , more preferably 3 to 7 μm . If a finer particle fraction is present the proportion of finer excipient in the total amount of excipient is 1 to 20 %, preferably 3 to 15%, more preferably 5 to 10%.

When reference is made to a mixture within the scope of the present invention, this always means a mixture obtained by mixing together clearly defined components. Accordingly, when an excipient mixture of coarser and finer excipients is mentioned, this can only denote mixtures obtained by mixing a coarser excipient component with 5 a finer excipient component.

The percentages given within the scope of the present invention are always percent by weight.

10 In the method according to the invention the inhalable powders mentioned hereinbefore may efficiently be administered using inhalers that are characterized by a specific flow resistance (R).

The flow resistance of inhalers can be calculated via the following formula:

15

$$v = \frac{1}{R} \cdot \sqrt{p}$$

wherein v is the volumetric flow rate (l/min),
p is the pressure drop (kPa), and

20 R is the flow resistance.

In the method according to the invention the flow resistance R characterising the inhaler is in a range of about $0.01 - 0.1 \sqrt{kPa}$ min/l preferably in the range of about 0.02 – 0.06 \sqrt{kPa} min/l.

25

Accordingly, the invention relates to a method for the administration of an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , and further characterized in that the said tiotropium containing powder 30 is administered by an inhaler displaying a flow resistance of about $0.01 - 0.1 \sqrt{kPa}$ min/l.

In another embodiment, the invention relates to a method for the treatment of airway diseases, particularly COPD (chronic obstructive pulmonary disease) and asthma, 35 characterized in that an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , is administered via inhalation by an inhaler displaying a flow resistance of about $0.01 - 0.1 \sqrt{kPa}$ min/l.

In another embodiment the invention relates to the use of an inhaler for the administration of a tiotropium containing inhalable powder via inhalation, characterised in that the inhalable powder contains tiotropium, preferably in an

5 amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , and further characterized in that the said inhaler displays a flow resistance of about $0.01 - 0.1 \sqrt{\text{kPa}} \text{ min/l}$.

In yet another embodiment the invention relates to an inhalation kit consisting of an

10 inhaler displaying a flow resistance of about $0.01 - 0.1 \sqrt{\text{kPa}} \text{ min/l}$ and an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm .

15 In another preferred embodiment according to the invention the inhaler described in Figure 1 is applied. For the administration of tiotropium containing powders by inhalation by means of the inhaler according to figure 1, it is required to fill appropriate amounts of the powder into capsules. Methods for filling powders into capsules are known in the art.

20 The inhaler according to figure 1 is characterised by a housing 1 containing two windows 2, a deck 3 in which there are air inlet ports and which is provided with a screen 5 secured via a screen housing 4, an inhalation chamber 6 connected to the deck 3 on which there is a push button 9 provided with two sharpened pins 7 and movable counter to a spring 8, a mouthpiece 12 which is connected to the housing 1,

25 the deck 3 and a cover 11 via a spindle 10 to enable it to be flipped open or shut and three holes 13 with diameters below 1 mm in the central region around the capsule chamber 6 and underneath the screen housing 4 and screen 5.

The main air flow enters the inhaler between deck 3 and base 1 near to the hinge. The deck has in this range a reduced width, which forms the entrance slit for the air.

30 Then the flow reverses and enters the capsule chamber 6 through the inlet tube. The flow is then further conducted through the filter and filter holder to the mouthpiece. A small portion of the flow enters the device between mouthpiece and deck and flows then between filterholder and deck into the main stream. Due to production tolerances there is some uncertainty in this flow because of the actual width of the

35 slit between filterholder and deck. In case of new or reworked tools the flow resistance of the inhaler may therefore be a little off the target value. To correct this deviation the deck has in the central region around the capsule chamber 6 and underneath the screen housing 4 and screen 5 three holes 13 with diameters below 1 mm. Through these holes 13 flows air from the base into the main air stream and

reduces such slightly the flow resistance of the inhaler. The actual diameter of these holes 13 can be chosen by proper inserts in the tools so that the mean flow resistance can be made equal to the target value.

- 5 Accordingly, in a preferred embodiment the invention relates to a method for the administration of an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , by means of the inhaler according to figure 1, comprising
 - 10 a housing, containing two windows, a deck in which there are air inlet ports and which is provided with a screen secured via a screen housing, an inhalation chamber connected to the deck on which there is a push button provided with two sharpened pins and movable counter to a spring, a mouthpiece which is connected to the housing, the deck and a cover via a spindle to enable it to be flipped open or shut,
 - 15 and three holes with diameters below 1 mm in the central region around the capsule chamber and underneath the screen housing and screen.

- 20 In another embodiment, the invention relates to a method for treatment of airway diseases, particularly COPD (chronic obstructive pulmonary disease) and asthma, characterized in that an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , is administered via inhalation by the inhaler according to figure 1, comprising
 - 25 a housing, containing two windows, a deck in which there are air inlet ports and which is provided with a screen secured via a screen housing, an inhalation chamber connected to the deck on which there is a push button provided with two sharpened pins and movable counter to a spring, a mouthpiece which is connected to the housing, the deck and a cover via a spindle to enable it to be flipped open or shut,
 - 30 and three holes with diameters below 1 mm in the central region around the capsule chamber and underneath the screen housing and screen.

- 35 In another preferred embodiment the invention relates to the use of the inhaler according to figure 1, comprising a housing, containing two windows, a deck in which there are air inlet ports and which is provided with a screen secured via a screen housing, an inhalation chamber connected to the deck on which there is a push button provided with two sharpened pins and movable counter to a spring; a mouthpiece which is connected to the housing, the deck and a cover via a spindle to enable it to be flipped open or shut, and three holes with diameters below 1 mm in

the central region around the capsule chamber and underneath the screen housing and screen,
for the administration of an inhalable powdered containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient
5 with an average particle size of between 10 to 500 μm .

In yet another preferred embodiment the invention relates to an inhalation kit consisting of an inhalable powdered containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an
10 average particle size of between 10 to 500 μm , and the inhaler according to figure 1, comprising
a housing, containing two windows, a deck in which there are air inlet ports and which is provided with a screen secured via a screen housing, an inhalation chamber connected to the deck on which there is a push button provided with two sharpened
15 pins and movable counter to a spring, a mouthpiece which is connected to the housing, the deck and a cover via a spindle to enable it to be flipped open or shut, and three holes with diameters below 1 mm in the central region around the capsule chamber and underneath the screen housing and screen.
20 In another preferred embodiment according to the invention the inhaler according to US 4,524,769 is applied. This inhaler (or inhalator) is activated by the air flow generated at inhalation. The disclosure of US 4,524,769 is incorporated herein by reference in its entirety.
25 Accordingly, in a preferred embodiment the invention relates to a method for the administration of an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , by means of the inhaler according to US 4,524,769, comprising a nozzle, a conduit connected to the nozzle,
30 a storage chamber adjacent said conduit for storing said inhalable powder to be dispensed by said inhalator, a perforated membrane having a plurality of preselected perforated portions each holding and dispensing a reproducible unit dose of less than 50 mg of the said inhalable powder, said membrane being mounted for movement between said conduit and said storage chamber so that one of said
35 preselected portions is positioned across said conduit whereby the active compound held in the perforation thereof can be dispensed into the conduit and another of said preselected portions thereof is disposed within said storage chamber, dose loading means for introducing said inhalable powder in the storage chamber into the perforation of the preselected portion of said membrane disposed within the

storage chamber, and maneuvering means for displacing the perforated membrane through a plurality of positions whereby successive preselected portions of the perforated membrane holding the inhalable powder are positioned across said conduit for dispensing the inhalable powder.

5

In another embodiment, the invention relates to a method for treatment of airway diseases, particularly COPD (chronic obstructive pulmonary disease) and asthma, characterized in that an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , is administered via inhalation by the inhaler according to US 4,524,769, comprising a nozzle, a conduit connected to the nozzle, a storage chamber adjacent said conduit for storing said inhalable powder to be dispensed by said inhalator, a perforated membrane having a plurality of preselected perforated portions each holding and dispensing a reproducible unit dose of less than 50 mg of the said inhalable powder, said membrane being mounted for movement between said conduit and said storage chamber so that one of said preselected portions is positioned across said conduit whereby the active compound held in the perforation thereof can be dispensed into the conduit and another of said preselected portions thereof is disposed within said storage chamber, dose loading means for introducing said inhalable powder in the storage chamber into the perforation of the preselected portion of said membrane disposed within the storage chamber, and maneuvering means for displacing the perforated membrane through a plurality of positions whereby successive preselected portions of the perforated membrane holding the inhalable powder are positioned across said conduit for dispensing the inhalable powder.

In another preferred embodiment the invention relates to the use of the inhaler according to US 4,524,769 comprising a nozzle, a conduit connected to the nozzle, a storage chamber adjacent said conduit for storing said inhalable powder to be dispensed by said inhalator, a perforated membrane having a plurality of preselected perforated portions each holding and dispensing a reproducible unit dose of less than 50 mg of the said inhalable powder, said membrane being mounted for movement between said conduit and said storage chamber so that one of said preselected portions is positioned across said conduit whereby the active compound held in the perforation thereof can be dispensed into the conduit and another of said preselected portions thereof is disposed within said storage chamber, dose loading means for introducing said inhalable powder in the storage chamber into the perforation of the preselected

portion of said membrane disposed within the storage chamber, and maneuvering means for displacing the perforated membrane through a plurality of positions whereby successive preselected portions of the perforated membrane holding the inhalable powder are positioned across said conduit for dispensing the

5 inhalable powder,

for the administration of an inhalable powdered containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm .

10 In yet another preferred embodiment the invention relates to an inhalation kit consisting of an inhalable powdered containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , and the inhaler according to US 4,524,769, comprising

15 a nozzle, a conduit connected to the nozzle, a storage chamber adjacent said conduit for storing said inhalable powder to be dispensed by said inhalator, a perforated membrane having a plurality of preselected perforated portions each holding and dispensing a reproducible unit dose of less than 50 mg of the said inhalable powder, said membrane being mounted for movement between said conduit

20 and said storage chamber so that one of said preselected portions is positioned across said conduit whereby the active compound held in the perforation thereof can be dispensed into the conduit and another of said preselected portions thereof is disposed within said storage chamber, dose loading means for introducing said inhalable powder in the storage chamber into the perforation of the preselected

25 portion of said membrane disposed within the storage chamber, and maneuvering means for displacing the perforated membrane through a plurality of positions whereby successive preselected portions of the perforated membrane holding the inhalable powder are positioned across said conduit for dispensing the inhalable powder.

30 In another preferred embodiment according to the invention the inhaler according to US 5,590,645 is applied. The disclosure of US 5,590,645 is incorporated herein by reference in its entirety.

35 Accordingly, in a preferred embodiment the invention relates to a method for the administration of an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , by means of the inhaler according to 5,590,645, comprising

a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are spaced along the length of and defined between two peelable sheets secured to each other, an opening station for receiving a container of said medicament pack being, means positioned to engage peelable sheets of a container which has been received in said opening station for peeling apart the peelable sheets, to open such a container, an outlet, positioned to be in communication with an opened container, through which a user can inhale medicament in powder form from such an opened container, and indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device.

In another embodiment, the invention relates to a method for treatment of airway diseases, particularly COPD (chronic obstructive pulmonary disease) and asthma, characterized in that an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , is administered via inhalation by the inhaler according to US 5,590,645, comprising a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are spaced along the length of and defined between two peelable sheets secured to each other, an opening station for receiving a container of said medicament pack being, means positioned to engage peelable sheets of a container which has been received in said opening station for peeling apart the peelable sheets, to open such a container, an outlet, positioned to be in communication with an opened container, through which a user can inhale medicament in powder form from such an opened container, and indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device.

In another preferred embodiment the invention relates to the use of the inhaler according to US 5,590,645, comprising a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are spaced along the length of and defined between two peelable sheets secured to each other, an opening station for receiving a container of said medicament pack being, means positioned to engage peelable sheets of a container which has been received in said opening station for peeling apart the peelable sheets, to open such a container, an outlet, positioned to be in communication with an opened container, through which a user can inhale medicament in powder form from such an opened container, and

indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device,
for the administration of an inhalable powdered containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient
5 with an average particle size of between 10 to 500 μm .

In yet another preferred embodiment the invention relates to an inhalation kit consisting of an inhalable powdered containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an
10 average particle size of between 10 to 500 μm , and the inhaler according to US 5,590,645, comprising
a medicament pack having a plurality of containers for containing medicament in powder form wherein the containers are spaced along the length of and defined between two peelable sheets secured to each other, an opening station for receiving
15 a container of said medicament pack being, means positioned to engage peelable sheets of a container which has been received in said opening station for peeling apart the peelable sheets, to open such a container, an outlet, positioned to be in communication with an opened container, through which a user can inhale medicament in powder form from such an opened container, and
20 indexing means for indexing in communication with said outlet containers of a medicament pack in use with said inhalation device.

In another preferred embodiment according to the invention the inhaler according to US 4,627,432 is applied. The disclosure of US 4,627,432 is incorporated herein by reference in its entirety.
25

Accordingly, in a preferred embodiment the invention relates to a method for the administration of an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an
30 average particle size of between 10 to 500 μm , by means of the inhaler according to US 4,627,432, being characterised by a housing with a chamber therein, an air inlet into the chamber,
a circular disc having an axis substantially coaxial to the chamber axis and rotatable inside the chamber and provided with a plurality of apertures therethrough arranged
35 in a circle, said apertures being sized and positioned so that each aperture is adapted to be aligned with a different container, the said disc being arranged so that the carrier can be placed in contact with one face of the disc with one of the containers located in each one of the apertures, an outlet through which a patient may inhale leading out of the chamber, an opening in said housing alignable with

respective ones of the apertures in the disc as the disc is rotated, a plunger operatively connected to said housing and having a penetrating member, said penetrating member being displaceable to pass through said opening and the corresponding aperture in the disc registered with it thereby to penetrate and open a container located in the aperture so that the medicament will be released from the container and entrained in the air flow produced by a patient inhaling through the outlet, and means between said disc and said housing for rotatably indexing the disc to register each of the apertures in turn with the housing opening.

10 In another embodiment, the invention relates to a method for treatment of airway diseases, particularly COPD (chronic obstructive pulmonary disease) and asthma, characterized in that an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , is administered via inhalation by

15 the inhaler according to US 4,627,432, being characterised by a housing with a chamber therein, an air inlet into the chamber, a circular disc having an axis substantially coaxial to the chamber axis and rotatable inside the chamber and provided with a plurality of apertures therethrough arranged in a circle, said apertures being sized and positioned so that each aperture is

20 adapted to be aligned with a different container, the said disc being arranged so that the carrier can be placed in contact with one face of the disc with one of the containers located in each one of the apertures, an outlet through which a patient may inhale leading out of the chamber, an opening in said housing alignable with respective ones of the apertures in the disc as the disc is rotated, a plunger

25 operatively connected to said housing and having a penetrating member, said penetrating member being displaceable to pass through said opening and the corresponding aperture in the disc registered with it thereby to penetrate and open a container located in the aperture so that the medicament will be released from the container and entrained in the air flow produced by a patient inhaling through the

30 outlet, and means between said disc and said housing for rotatably indexing the disc to register each of the apertures in turn with the housing opening.

In another preferred embodiment the invention relates to the use of the inhaler according to US 4,627,432 being characterised by a housing with a chamber therein, an air inlet into the chamber, a circular disc having an axis substantially coaxial to the chamber axis and rotatable inside the chamber and provided with a plurality of apertures therethrough arranged in a circle, said apertures being sized and positioned so that each aperture is adapted to be aligned with a different container, the said disc being arranged so that

the carrier can be placed in contact with one face of the disc with one of the containers located in each one of the apertures, an outlet through which a patient may inhale leading out of the chamber, an opening in said housing alignable with respective ones of the apertures in the disc as the disc is rotated, a plunger

5 operatively connected to said housing and having a penetrating member, said penetrating member being displaceable to pass through said opening and the corresponding aperture in the disc registered with it thereby to penetrate and open a container located in the aperture so that the medicament will be released from the container and entrained in the air flow produced by a patient inhaling through the

10 outlet, and means between said disc and said housing for rotatably indexing the disc to register each of the apertures in turn with the housing opening, for the administration of an inhalable powdered containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm .

15

In yet another preferred embodiment the invention relates to an inhalation kit consisting of an inhalable powdered containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , and the inhaler according to US

20 4,627,432, being characterised by a housing with a chamber therein, an air inlet into the chamber,

a circular disc having an axis substantially coaxial to the chamber axis and rotatable inside the chamber and provided with a plurality of apertures therethrough arranged in a circle, said apertures being sized and positioned so that each aperture is

25 adapted to be aligned with a different container, the said disc being arranged so that the carrier can be placed in contact with one face of the disc with one of the containers located in each one of the apertures, an outlet through which a patient may inhale leading out of the chamber, an opening in said housing alignable with respective ones of the apertures in the disc as the disc is rotated, a plunger

30 operatively connected to said housing and having a penetrating member, said penetrating member being displaceable to pass through said opening and the corresponding aperture in the disc registered with it thereby to penetrate and open a container located in the aperture so that the medicament will be released from the container and entrained in the air flow produced by a patient inhaling through the

35 outlet, and means between said disc and said housing for rotatably indexing the disc to register each of the apertures in turn with the housing opening.

The following Examples serve to illustrate the present invention further without restricting its scope to the embodiments provided hereinafter by way of example.

Starting materials

As a starting material for the synthesis of crystalline tiotropiumbromide monohydrate tiotropiumbromide obtained according to the disclosure of European patent 5 application EP 418 716 A1 is be used.

Preparation of crystalline tiotropium bromide monohydrate:

15.0 kg of tiotropium bromide as obtained according to the methods disclosed in EP 418 716 A1 are added to 25.7 kg of water in a suitable reaction vessel. The mixture 19 is heated to 80-90°C and stirred at constant temperature until the clear solution is formed. Activated charcoal (0.8 kg), moistened with water, is suspended in 4.4 kg of water, this mixture is added to the solution containing the tiotropium bromide and rinsed with 4.3 kg of water. The mixture thus obtained is stirred for at least 15 min at 80-90°C and then filtered through a heated filter into an apparatus which has been 15 preheated to an outer temperature of 70°C . The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled at 3-5°C every 20 minutes to a temperature of 20-25°C. The apparatus is further cooled to 10-15°C using cold water and crystallisation is completed by stirring for at least one hour. The crystals are 20 isolated using a suction drier, the crystal slurry isolated is washed with 9 litres of cold water (10-15°C) and cold acetone (10-15°C). The crystals obtained are dried in a nitrogen current at 25°C over 2 hours.

Yield : 13.4 kg of tiotropium bromide monohydrate (86 % of theory)

25 The crystalline tiotropium bromide monohydrate thus obtained is micronised by known methods, to bring the active substance into the average particle size which meets the specifications according to the invention.

30 The DSC diagram of crystalline tiotropium bromide monohydrate shows two characteristic signals. The first, relatively broad, endothermic signal between 50- 120°C can be attributed to the dehydration of the tiotropium bromide monohydrate to produce the anhydrous form. The second, relatively sharp endothermic peak at 230 ± 5°C can be put down to the melting of the substance. These data were obtained using a Mettler DSC 821 and evaluated with the Mettler STAR software package. These data, like the other values given in the above Table, were obtained at a 35 heating rate of 10 K/min.

The crystalline tiotropium bromide monohydrate thus obtained was characterised by IR spectroscopy. The data was obtained using a Nicolet FTIR spectrometer and

evaluated with the Nicolet OMNIC software package, version 3.1. The measurement was carried out with 2.5 μ mol of tiotropium bromide monohydrate in 300 mg of KBr. Table 1 shows some of the essential bands of the IR spectrum.

5 Table 1: Attribution of specific bands

Wave number (cm ⁻¹)	Attribution	Type of oscillation
3570, 410	O-H	elongated oscillation
3105	Aryl C-H	elongated oscillation
1730	C=O	elongated oscillation
1260	Epoxide C-O	elongated oscillation
1035	Ester C-OC	elongated oscillation
720	Thiophene	cyclic oscillation

10 The crystalline tiotropium bromide monohydrate was characterised by X-ray structural analysis. The measurements of X-ray diffraction intensity were carried out on an AFC7R- 4-circuit diffractometer (Rigaku) using monochromatic copper K α radiation. The structural solution and refinement of the crystal structure were obtained by direct methods (SHELXS86 Program) and FMLQ-refinement (TeXsan Program). The X-ray structural analysis carried out showed that crystalline tiotropium bromide hydrate has a simple monoclinic cell with the following dimensions:
15 a = 18.0774 Å, b = 11.9711 Å, c = 9.9321 Å, β = 102.691°, V = 2096.96 Å³.

Apparatus

20 The following machines and equipment, for example, may be used to prepare the inhalable powders according to the invention:

Mixing container or powder mixer: Gyrowheel mixer 200 L; type: DFW80N-4; made by: Messrs Engelsmann, D-67059 Ludwigshafen.

25 Granulating sieve: Quadro Comil; type: 197-S; made by: Messrs Joisten & Kettenbaum, D-51429 Bergisch-Gladbach.

The following examples provide for inhalable powder mixtures applicable according to the invention.

Example 1:

5 5.2 kg of glucose monohydrate for inhalation (average particle size 25 μ m) are used as the excipient. 22.5 g crystalline tiotropiumbromide monohydrate (micronised; average particle size 1 - 3.5 μ m) are used as the active ingredient.

10 The aforementioned components are sieved in in alternate layers of lactose monohydrate in batches of about 200 g and crystalline tiotropiumbromide monohydrate in batches of about 1g. The ingredients sieved in are then mixed together (mixing at 900 rpm).

15 According to the invention preferably 5.2225 mg of the aforementioned powder are delivered per dose.

Example 2:

20 5.4775 kg of lactose monohydrate for inhalation (average particle size 25 μ m) are used as the excipient. 22.5 g crystalline tiotropiumbromide monohydrate (micronised; average particle size 1 - 3.5 μ m) are used as the active ingredient.

25 The aforementioned components are sieved in in alternate layers of lactose monohydrate in batches of about 200 g and crystalline tiotropiumbromide monohydrate in batches of about 1g. The ingredients sieved in are then mixed together (mixing at 900 rpm).

According to the invention preferably 5.5 mg of the aforementioned powder are delivered per dose.

30 **Example 3:**

1.1: Excipient mixture:

35 5.203 kg of lactose monohydrate for inhalation (average particle size 25 μ m) are used as the coarser excipient component. 0,27 kg of lactose monohydrate (5 μ m) are used as the finer excipient component. In the resulting 5,473 kg of excipient mixture the proportion of the finer excipient component is 5%.

The aforementioned components are sieved in in alternate layers of lactose monohydrate (25 μ m) in batches of about 200 g and lactose monohydrate (5 μ m) in

batches of about 10g. The ingredients sieved in are then mixed together (mixing at 900 rpm).

1.2: Final mixture:

5 To prepare the final mixture, 5,473 kg of the excipient mixture (1.1) and 22.5 g crystalline tiotropiumbromide monohydrate (micronised; average particle size 1 - 3.5 μ m) are used. The content of active substance in the resulting powder is 0.4%.

10 The aforementioned components are sieved in in alternate layers of excipient mixture (1.1) in batches of about 200 g and crystalline tiotropiumbromide monohydrate in batches of about 1g. The ingredients sieved in are then mixed together (mixing at 900 rpm).

15 According to the invention preferably about 5.5 mg of the aforementioned powder are delivered per dose.

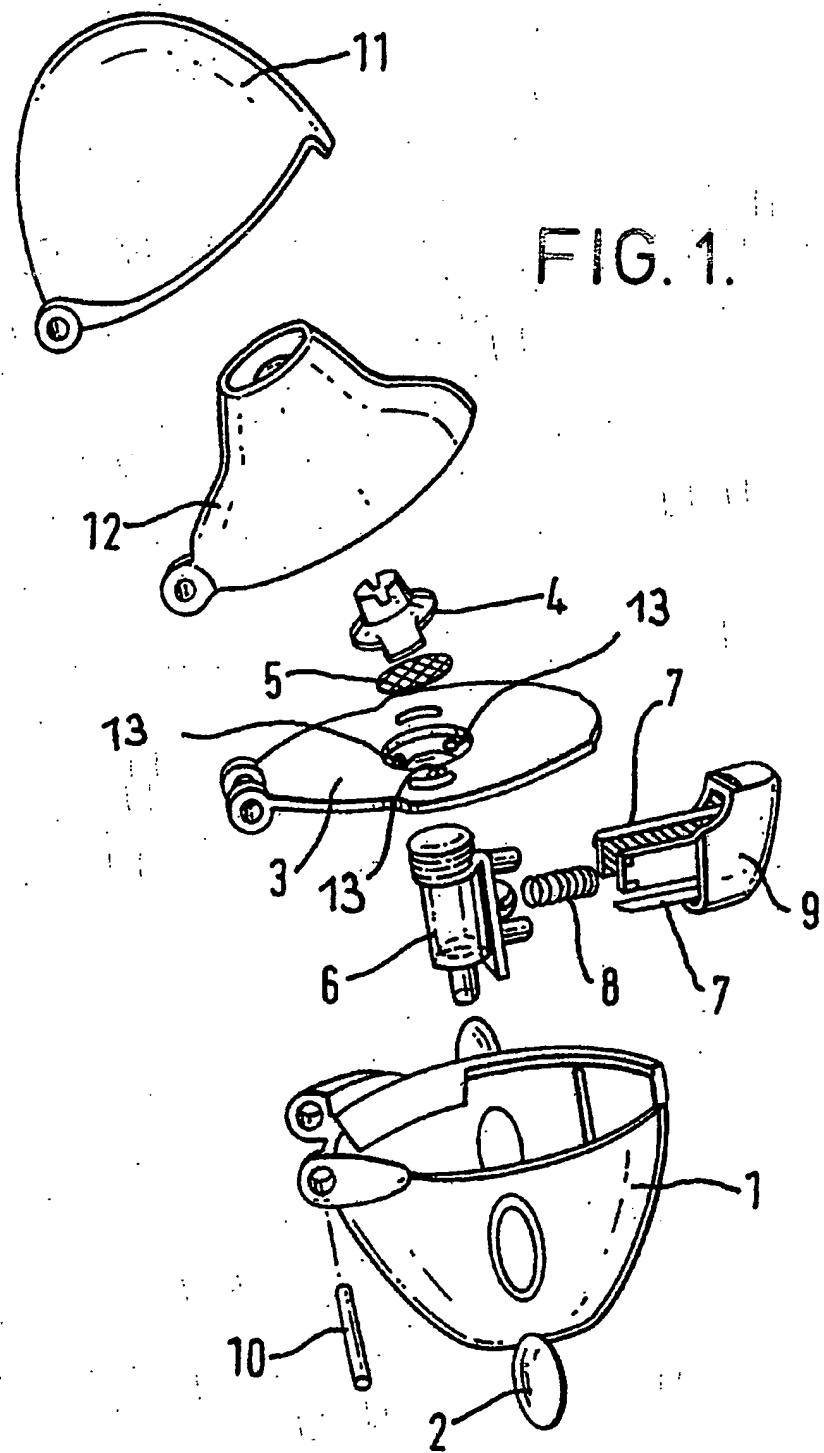
Patent Claims

- 1) Use of an inhaler for the administration of a tiotropium containing inhalable powder via inhalation, characterised in that the inhalable powder contains tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm , and further characterized in that the said inhaler displays a flow resistance of about $0.01 - 0.1 \sqrt{\text{kPa}} \text{ min/l}$.
- 10 2) Use according to claim 1, characterised in that the inhaler is characterized by a flow resistance of about $0.02 - 0.06 \sqrt{\text{kPa}} \text{ min/l}$.
- 15 3) Use according to claim 1 or 2, characterised in that the inhaler comprises a housing, containing two windows, a deck in which there are air inlet ports and which is provided with a screen secured via a screen housing, an inhalation chamber connected to the deck on which there is a push button provided with two sharpened pins and movable counter to a spring, a mouthpiece which is connected to the housing, the deck and a cover via a spindle to enable it to be flipped open or shut, and three holes with diameters below 1 mm in the central 20 region around the capsule chamber and underneath the screen housing and screen.
- 25 4) Use according to one of claims 1, 2 or 3, characterised in that tiotropium is used in form of its chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate, preferably in form of its bromide.
- 5) Use according to claim 4, characterised in that tiotropium is used in form of its crystalline tiotropium bromide monohydrate.
- 30 6) Inhalation kit consisting of an inhaler displaying a flow resistance of about $0.01 - 0.1 \sqrt{\text{kPa}} \text{ min/l}$ and an inhalable powder containing tiotropium, preferably in an amount of 0.001 to 5 %, in admixture with a physiologically acceptable excipient with an average particle size of between 10 to 500 μm .
- 35 7) Inhalation kit according to claim 6, characterised in that the inhaler is characterized by a flow resistance of about $0.02 - 0.06 \sqrt{\text{kPa}} \text{ min/l}$.

8) Inhalation kit according to claim 6 or 7, characterised in that the inhaler comprises a housing, containing two windows, a deck in which there are air inlet ports and which is provided with a screen secured via a screen housing, an inhalation chamber connected to the deck on which there is a push button provided with two sharpened pins and movable counter to a spring, a mouthpiece which is connected to the housing, the deck and a cover via a spindle to enable it to be flipped open or shut, and three holes with diameters below 1 mm in the central region around the capsule chamber and underneath the screen housing and screen.

10 9) Inhalation kit according to one of claims 6, 7 or 8, characterised in that tiotropium is present in form of its chloride, bromide, iodide, methanesulphonate, para-toluenesulphonate or methyl sulphate, preferably in form of its bromide.

15 10) Inhalation kit according to claim 9, characterised in that tiotropium is present in form of its crystalline tiotropium bromide monohydrate.



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03431

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K31/46 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 28979 A (SKYEPHARMA AG ;MUELLER WALZ RUDI (DE); KELLER MANFRED (DE)) 25 May 2000 (2000-05-25) page 18, line 26 -page 18, line 31; example 6	1-10
X	EP 1 158 970 A (NOVARTIS ERFIND VERWALT GMBH ;NOVARTIS AG (CH)) 5 December 2001 (2001-12-05) example 3	1-10
Y	US 5 590 645 A (DAVIES MICHAEL BIRSHA ET AL) 7 January 1997 (1997-01-07) figures 1-34	1-10
Y	US 4 627 432 A (NEWELL ROBERT E ET AL) 9 December 1986 (1986-12-09) figures 1-4	1-10
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *a* document member of the same patent family

Date of the actual completion of the international search

14 July 2003

Date of mailing of the international search report

25/07/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

ESTANOL, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03431

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 524 769 A (WETTERLIN KJELL I L) 25 June 1985 (1985-06-25) figures 1,2	1-10
A	US 6 182 655 B1 (EGGIMANN THOMAS ET AL) 6 February 2001 (2001-02-06) figures 1-23	1-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/03431

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: _____
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT – Method for treatment of the human or animal body by therapy
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.: _____
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: _____

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/03431

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 0028979	A 25-05-2000		AT 233550 T AU 756852 B2 AU 6457899 A CA 2347856 A1 WO 0028979 A1 CN 1326341 T CZ 20011553 A3 DE 59904488 D1 EP 1283036 A1 EP 1131059 A1 HU 0104226 A2 JP 2002529498 T NO 20012346 A NZ 511527 A PL 347640 A1 SK 6322001 A3 ZA 200103627 A	15-03-2003 23-01-2003 05-06-2000 25-05-2000 25-05-2000 12-12-2001 12-09-2001 10-04-2003 12-02-2003 12-09-2001 28-02-2002 10-09-2002 26-06-2001 25-10-2002 22-04-2002 07-01-2002 09-05-2001
EP 1158970	A 05-12-2001		AU 2441900 A BR 0008039 A CA 2360248 A1 EP 1158970 A1 JP 2002536408 T NO 20013460 A NZ 513304 A PL 350583 A1 SK 11272001 A3 US 6537524 B1 CN 1338928 T CZ 20012856 A3 WO 0047200 A1 HU 0200083 A2 TR 200102226 T2	29-08-2000 06-11-2001 17-08-2000 05-12-2001 29-10-2002 13-09-2001 31-01-2003 13-01-2003 03-12-2001 25-03-2003 06-03-2002 14-11-2001 17-08-2000 29-06-2002 21-01-2002
US 5590645	A 07-01-1997		AP 310 A US 2002066451 A1 US 6032666 A US 6378519 B1 US 2002053344 A1 AT 401007 B AT 43791 A AU 675825 B2 AU 5926794 A AU 645056 B2 AU 7202591 A BE 1003798 A4 BR 9100843 A CA 2037421 A1 CH 683319 A5 CN 1054893 A ,B CN 1107687 A ,B CZ 283168 B6 CZ 9601807 A3 CY 2010 A CY 2014 A CZ 285501 B6 DE 4106379 A1 DK 37991 A	07-01-1994 06-06-2002 07-03-2000 30-04-2002 09-05-2002 28-05-1996 15-10-1995 20-02-1997 16-06-1994 06-01-1994 05-09-1991 16-06-1992 05-11-1991 03-09-1991 28-02-1994 02-10-1991 06-09-1995 14-01-1998 16-12-1998 20-02-1998 20-02-1998 11-08-1999 05-09-1991 03-09-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/03431

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5590645	A	ES 2031763 A6	16-12-1992
		FI 911037 A	03-09-1991
		FI 990115 A	21-01-1999
		FR 2659558 A1	20-09-1991
		FR 2660550 A1	11-10-1991
		GB 2242134 A ,B	25-09-1991
		GB 2274273 A ,B	20-07-1994
		GR 91100096 A ,B	30-06-1992
		HK 18895 A	17-02-1995
		HK 19195 A	17-02-1995
		HR 940631 A1	31-08-1996
		IE 910698 A1	11-09-1991
		IL 97396 A	31-12-1995
		IT 1244655 B	08-08-1994
		JP 3110477 B2	20-11-2000
		JP 4220266 A	11-08-1992
		KR 210412 B1	15-07-1999
		KR 244004 B1	15-03-2000
		LU 87898 A1	16-11-1992
		NL 9100381 A ,B,	01-10-1991
		NO 910836 A	03-09-1991
		NO 302929 B1	11-05-1998
		NO 980033 A	05-01-1998
		NZ 237274 A	27-02-1996
		NZ 260140 A	27-02-1996
		PL 289264 A1	01-06-1992
US 4627432	A 09-12-1986	AT 396333 B	25-08-1993
		AT 357683 A	15-12-1992
		AU 570013 B2	03-03-1988
		AU 1997783 A	12-04-1984
		AU 584535 B2	25-05-1989
		AU 8315587 A	21-04-1988
		BE 897946 A1	09-04-1984
		BR 8305562 A	15-05-1984
		CA 1224992 A1	04-08-1987
		CA 1236736 A2	17-05-1988
		CH 662277 A5	30-09-1987
		CY 1477 A	21-07-1989
		CY 1478 A	21-07-1989
		DE 3336486 A1	26-04-1984
		DE 3348370 C2	11-10-2001
		DK 45198 A	20-12-1999
		DK 464383 A	09-04-1984
		ES 286422 U	01-02-1986
		FI 833641 A ,B,	09-04-1984
		FI 891175 A ,B,	13-03-1989
		FR 2550452 A1	15-02-1985
		FR 2570607 A1	28-03-1986
		GB 2129691 A ,B	23-05-1984
		GB 2169265 A ,B	09-07-1986
		GR 79615 A1	31-10-1984
		HK 67689 A	01-09-1989
		HK 67789 A	01-09-1989
		IE 56059 B1	10-04-1991
		IE 56060 B1	10-04-1991
		IL 69932 A	31-12-1987
		IL 80468 A	30-11-1987

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/03431

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 4627432	A		IN 160851 A1 IT 1203660 B JP 59088158 A JP 1888266 C JP 5076872 B JP 5200100 A KE 3860 A KE 3861 A KR 9102248 B1 LU 85034 A1 NL 8303461 A ,B, NL 9700002 A ,B, RO 833667 A ,B, NZ 205892 A NZ 218860 A PT 77471 A ,B SE 458824 B SE 8305542 A SE 465752 B	08-08-1987 15-02-1989 22-05-1984 07-12-1994 25-10-1993 10-08-1993 02-06-1989 02-06-1989 08-04-1991 19-06-1985 01-05-1984 02-06-1997 09-04-1984 31-07-1987 26-04-1989 01-11-1983 16-05-1989 09-04-1984 28-10-1991
US 4524769	A	25-06-1985	AT 23272 T AU 559297 B2 AU 8560882 A CA 1178151 A1 CY 1492 A DE 3274065 D1 DK 304482 A ,B, EG 16516 A EP 0069715 A1 ES 276079 U FI 822423 A ,B, FI 882983 A ,B, GR 76522 A1 HK 64389 A HR 921331 B1 HU 189154 B IE 53933 B1 IL 66053 A IN 158972 A1 JP 1047190 B JP 1563122 C JP 58019269 A KE 3890 A KR 8801811 B1 NO 822370 A ,B, NO 860142 A NO 157205 B NZ 201154 A PH 22387 A PL 237363 A1 PT 75211 A ,B SG 37089 G SI 8211414 A8 YU 141482 A1 ZA 8204264 A	15-11-1986 05-03-1987 13-01-1983 20-11-1984 16-02-1990 11-12-1986 09-01-1983 30-06-1992 12-01-1983 01-05-1984 09-01-1983 22-06-1988 10-08-1984 18-08-1989 30-04-1996 30-06-1986 26-04-1989 30-10-1987 28-02-1987 12-10-1989 12-06-1990 04-02-1983 01-09-1989 19-09-1988 10-01-1983 10-01-1983 02-11-1987 24-08-1984 12-08-1988 28-02-1983 01-08-1982 13-10-1989 31-08-1995 30-04-1987 27-04-1983
US 6182655	B1	06-02-2001	AT 193455 T AU 718682 B2	15-06-2000 20-04-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/03431

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6182655	B1	AU 7617396 A	27-06-1997
		CA 2239292 A1	12-06-1997
		CA 2392466 A1	12-06-1997
		WO 9720589 A1	12-06-1997
		DE 59605366 D1	06-07-2000
		DK 865302 T3	02-10-2000
		EP 0865302 A1	23-09-1998
		EP 0995457 A1	26-04-2000
		ES 2148812 T3	16-10-2000
		GR 3034282 T3	29-12-2000
		JP 2000501013 T	02-02-2000
		NO 982516 A	27-07-1998
		NZ 322422 A	28-02-2000
		ZA 9610296 A	24-06-1997